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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,773	11/20/2003	Kurt Allen Josef	CEPH-2311	8378

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,773	JOSEF ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-49 and 51* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 5/20/05, claim 29 has been amended. Claims 29-51 remain pending. Applicants' arguments filed 5/20/05 have been considered and found persuasive in part. The rejection of claims 29-51 under 35 U.S.C. 112 second paragraph is withdrawn. The rejection of claim 50 under 35 U.S.C. 112 first paragraph is also withdrawn. However, the rejection of claims 29-49 and 51 under 35 U.S.C. §112 is maintained.

The abbreviation "**AD**" is used hereinbelow to denote Alzheimer's Disease.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-49 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims encompass treatment of neurodegenerative disease, stroke, and AD. The factors to consider in evaluating the need (or absence of need) for "undue experimentation"

are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. [*Ex parte Forman* (230 USPQ 546, 1986)]. Applicants data is limited to a showing that a few of the claimed compounds an inhibit calpain I in a cell-free assay. The reality is that, where protease inhibition is concerned, an attempt to extrapolate from such inhibition *in vitro* to therapy of one of the recited disorders is an exercise resulting in an "unpredictable" outcome. Consider the following:

- Chen, M. (*Frontiers in Bioscience* **3** A66-75, 1998) discusses the possible role of calpain in AD. As conveyed in the reference, there is evidence both for and against calpain acting as an *alpha*-secretase. (See, e.g., page 9, last paragraph). This reference neither "proves" nor disproves that one can "treat" Alzheimer's Disease with a calpain inhibitor. It does, however, raise considerable doubt as to whether calpain places a critical role in the progression of this disease. Given that there is uncertainty about whether calpain even plays a critical role in Alzheimer's Disease, it is fair to say that any therapeutic benefit of calpain inhibition is "unpredictable".

- Kavita (*J. Biol Chem* **270**, 27758-65, 1995) discloses (e.g., p. 27764) that P388D1 macrophage lysate contains a factor that protects precursor IL-1 *beta* protein from calpain proteolysis. This supports the proposition that if one has obtained data on inhibition of calpain in a cell-free system, one cannot necessarily predict the outcome of such inhibition if cellular constituents are present in an *in vitro* system. If extrapolation from a cell-free incubation mixture to a simple *in vitro* system is unpredictable, it stands to reason that extrapolation from a cell-free incubation mixture to physiological milieux would also be unpredictable.

- Harriman (*Journal of Pharmacology and Experimental Therapeutics* **294** (3) 1083-7, 2000) discloses (e.g., page 1087) that some compounds wth high potency to purified calpain were ineffective in reducing calpain activity in renal proximal tubules (RPT), and that this might be due to their limited uptake into RPT. Also stated (page 1087)

is the following: "No clear correlation was obtained between the inhibitory constants of calpain and cytoprotection".

- Saez-Torres (*Clinical and Experimental Immunology* **121**, 151, 2000 discloses that peptide T inhibits T cell activation and cytokine production, but that it was not effective *in vivo* to treat EAE (experimental automimmune encephalomyelitis). This supports the assertion that where inflammation neurodegenerative disorders are concerned, one cannot predict therapeutic efficacy on the basis of an *in vitro* assay. As disclosed in Shields (*Proc Natl Acad Sci* 95, 5768, 1998), calpain is upregulated and secreted by activated T cells. Thus, if compounds which are effective to inhibit activation of T cells are not effective to treat EAE, it stands to reason that one cannot "predict" the therapeutic efficacy of calpain inhibitors to treat EAE either. [See also the following references for evidence of a direct connection between calpain activity and activated T-cells: Schaecher, K (*Journal of Neuroimmunology* **129** (1-2) 1-9, 2002); Schaecher, K. E. (*Journal of Neuroimmunology* **119** (2) 333-42, 2001); Rock, M. T. (*Experimental Cell Research* **261** (1) 260-70, 2000)].

- Steinberg (*The Scientist* **16**, 22, 2002) discloses that when researchers vaccinated transgenic mice that had developed AD-like pathology, placques "melted away". In addition, favorable results were obtained in cognitive experiments with the mice. However, when attempted in humans, the Alzheimer's symptoms worsened. While the reference does not discuss calpain inhibition, the reference nevertheless supports an assertion of "unpredictability" in the treatment of AD. Applicants, for their part, have shown no evidence that any of the claimed compounds can be used to treat AD.

- Haas (*Journal of Leukocyte Biology* **63** (3) 395-404, 1998) discloses that calpain inhibitors were without effect in the inhibition of proinflammatory cytokine production. Haas supports the conclusion that if applicants' compounds were administered to an animal (or human) suffering from inflammation, proinflammatory cytokine production would continue unabated in spite of the presence of the compounds. Given that proinflammatory cytokine production will continue unabated, one cannot "predict" therapeutic efficacy in the treatment of inflammation using applicants' compounds. A similar conclusion arises from Rossi (*J Biol Chem* **273**, 16446, 1998) which discloses that the propensity of compounds to inhibit NF-*kappa* B cannot be predicted on the basis of their propensity to inhibit calpain.

In accordance with the foregoing, extrapolation from applicants' limited *in vitro* data to a therapy of any of the recited disorders is "unpredictable", and "undue experimentation" would be required to practice the claimed invention.

In response to Kavita (*J. Biol Chem* **270**, 27758-65, 1995) applicants have argued that calpain does not degrade IL-1 beta precursor protein *in vitro*. However, this is in contradiction to what is stated on page 27760, column 1. The issue raised by the examiner is that of the increasing complexity and "unpredictability" of extrapolating from an in vitro, cell-free system to an in vitro, cell-containing system, and from that to the intact physiological system. The complexities introduced in each of these extrapolations are far greater than applicants appear to realize (based on their rhetorical posture).

Next, applicants have commented on Harriman (*Journal of Pharmacology and Experimental Therapeutics* **294** (3) 1083-7, 2000). Applicants have argued that the failure of the compounds to inhibit calpain activity in renal proximal tubules might be due to the presence of other proteases or some other unidentified entity that hydrolyzed the substrate. At the same time, however, applicants are not willing to concede that other proteases are present within the human body (hundreds of them) which are insensitive to the compounds (to which the instant claims are directed) and which proteases can be just as deleterious as calpain. Applicants have not explained how they can predict which proteases will be inhibited and which will not. Further, the compounds (to which the

instant claims are directed) could easily be degraded by proteases or monooxygenases before they can get to the anatomical site where calpain inhibition might be beneficial.

Next, applicants have commented on Saez-Torres (*Clinical and Experimental Immunology* **121**, 151, 2000). Applicants have argued that peptide T is not a calpain inhibitor, and that calpain inhibitors do not inhibit T-cell activation. However, as conveyed in Schaecher, K.E., (*J Neuroimmunol* 119, 333-342, 2001), calpain does play a critical role in T-cell activation. With respect to the question of relevance of the references, the issue is one of competing extrapolations. In arguing that their compounds can be used to treat AD, applicants have merely pointed to references which suggest that calpain plays some sort of peripheral role. The examiner has not proven beyond all doubt that the subject compounds will fail to treat Alzheimer's and other neurodegenerative diseases. At the same time, applicants have not shown that the compounds can be used to treat AD (and applicants have not even attempted to argue that any other neurodegenerative disease can be successfully treated). The case for enablement or lack of enablement is based on the preponderance of the evidence. The examiner's extrapolation (to a conclusion of "unpredictability) based on the references which discuss T cell activation is no less relevant to the discussion than applicants' references which (according to applicants) support a conclusion of "predictability" in the treatment of Alzheimer's.

In attempting to dismiss Haas and Rossi, applicants have argued that they are not

claiming treatment of inflammation. However, whether applicants realize it or not, numerous inflammatory processes underlie all neurodegenerative processes. This is recognized by skilled neurologists, and moreover is asserted on a daily basis by patent applicants. If applicants are genuinely unaware of the contribution of inflammation in neurodegenerative diseases, it is suggested that applicants select one or two neurodegenerative diseases for which they believe inflammation does not contribute to progression thereof, and discussion on this issue can then begin.

In addition to the foregoing arguments, applicants have pointed to various references which show that other calpain inhibitors have exhibited efficacy in the treatment of ischemia if given before the ischemic event, or within a few hours thereafter. Even if it is true that the compounds (to which the claims are directed) are effective to treat ischemia or stroke, it does not follow therefrom that the compounds will be effective to treat AD. And certainly, there is no evidence to suggest that a calpain inhibitor exists which can treat any and all neurodegenerative diseases.

On the subject of AD, applicants have pointed to Jordan (*J Neurochem* **68**, 1612, 1997) who has shown that a calpain inhibitor was effective to inhibit Aβ- induced apoptosis of hippocampal pyramidal neurons in cell culture. Perhaps one can argue that enablement would exist for a claim that is drawn to a method of inhibiting Aβ- induced apoptosis of hippocampal pyramidal neurons (were such a process described in the specification).

However, even if such apoptosis can be inhibited, it does not follow therefrom that AD can be effectively treated. The reality is that all attempts to treat AD using calpain inhibitors have resulted in failure. Accordingly, it is not clear how it is that applicants can so confidently predict success in the treatment of this disease using the subject calpain inhibitors. Further, the Jordan reference can be used to support a conclusion of "unpredictability". Jordan examined the propensity of different calpain inhibitors to reduce the incidence of cell death induced by A-*beta*, staurosporine, and NMDA. It may be true that the inhibitor MDL 28,170 was effective *in vitro* in all three assays. But leupeptin was **not** effective in reducing the incidence of cell death induced by A-*beta* and staurosporine. This supports the proposition that, even if applicants could find a reference which showed that a given calpain inhibitor could be used to treat AD (and no such reference has been found), the argument could then be made (justifiably) that in treating AD, one cannot extrapolate from a finding of success with one calpain inhibitor to a proposed success with another.

Applicants' argument essentially is that (a) prior art disclosures permit one to assume that the compounds of the invention can be used to treat stroke, and (b) because calpain is somehow involved in the etiology of AD, this disease will yield to the compounds of the invention as well, and (c) because, in applicants' opinion, the subject compounds can be used to treat both stroke and Alzheimer's, it follows therefrom that any and all

neurodegenerative diseases can be successfully treated. Applicants' first point is now left unchallenged. The second assertion is not justified, but even if applicants could show that the disclosed compounds were indeed effective to treat AD, it would not follow therefrom that any and all neurodegenerative diseases could be successfully treated using the calpain inhibitors of the invention. Neurodegenerative diseases encompass the following:

> AIDS Dementia Complex (a.k.a. HIV-Associated Dementia) Amyotrophic Lateral Sclerosis (a.k.a. Lou Gehrig's Disease), Alzheimer 's Disease, Huntington's Disease, Multiple Sclerosis, Parkinson's Disease, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Creutzfeldt-Jakob disease, multifocal leukoencephalopathy, diffuse and transitional Lewy body disease, frontotemporal degeneration, corticobasal degeneration, multiple system atrophy, Pick Disease, argyrophilic grain disease and corticobasal degeneration. In addition, experimental automimmune encephalomyelitis is an animal model of multiple sclerosis.

Applicants may try to make the argument that because these diseases (with the exception of Alzheimer's) are not explicitly recited in the claims, the examiner should not be making any arguments with respect to them. However, what matters is what the claims encompass, and not simply that which is explicitly recited. Accordingly, all of the foregoing diseases are "fair game" for discussion. As it happens, attempts to treat these various diseases using calpain inhibitors have all met with failure. It is suggested that applicants go through the list of these diseases, and provide evidence (for each) to suggest that calpain inhibition will provide therapeutic relief to those suffering therefrom.

As matters currently stand, however, "undue experimentation" would be required to

practice the claimed invention.

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No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800